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Calculation of air supply rates for non-unidirectional airflow cleanrooms

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This article describes a method for estimating the air supply rate required in non-unidirectional airflow cleanrooms to obtain a required concentration of airborne particles and microbe-carrying particles. The variables considered are: surface deposition, emission rates of airborne contamination from personnel and machinery, filter removal efficiency, effectiveness of cleanroom garments, effectiveness of air supply distribution, and the contribution of filtered air from clean air devices. Consideration is also given to the variability of airborne contamination in cleanrooms, and the air supply rate required to ensure that the required airborne concentration will be rarely exceeded.

Key words: Calculation of air supply rates; airborne contamination; non-unidirectional airflow cleanrooms; airborne particles; microbe-carrying particles.

Introduction

Equations used to calculate the airborne concentration of particles and microbe-carrying particles (MCPs) in the build-up, steady-state and decay conditions in non-unidirectional cleanrooms have been discussed by Whyte *et al*¹. When a cleanroom is empty and no machinery running, the concentration of airborne contamination is practically zero, but as personnel enter and machines are switched on, the concentration builds up to a 'plateau' or 'steady state' that is maintained during manufacturing. There will be some variation in the steady-state concentration but the average airborne concentration can be calculated as follows.

Equation 1

$$C = D/Q_s$$

Where, C = airborne contamination concentration in the steady-state condition (number/m³), D = total dispersion rate of airborne contaminants from sources (number/s), and Q_s = air volume supply rate (m³/s).

Equation 1 assumes the supply air has passed through high efficiency air filters and contains few airborne particles. It also assumes that cleanrooms are positively pressurised, and no contamination enters from adjacent areas.

Equation 1 applies to small particles, typically $\geq 0.5 \mu\text{m}$, which do not deposit on surfaces in sufficient numbers to noticeably reduce the cleanroom's airborne concentration. However, larger particles, such as MCPs, which are dispersed on skin particles from personnel and have an average equivalent particle diameter of about $12 \mu\text{m}$ and an average deposition velocity of $4.6 \times 10^{-3} \text{ m/s}$ ^{2, 3} will deposit onto surfaces, and increase the apparent air change rate by about 5 to 6 per hour¹. In these circumstances, the following equation gives a more accurate result.

Equation 2

$$C = D/(Q_s + V_d \cdot A)$$

Where, V_d = deposition velocity in room air (0.0046m/s for MCPs), and A = area of surface deposition (normally the floor area).

By rearranging Equations 1 and 2, the air supply rate for a given concentration of small particles can be calculated as follows.

Equation 3

$$Q_s = \frac{D}{C}$$

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And for MCPs,

Equation 4

$$Q_s = \frac{D}{C} - V_D \cdot A$$

It should be noted that airborne cleanliness in a non-unidirectional airflow cleanroom is directly related to air volume supply rates, and not air change rates, which are additionally dependant on the volume of the cleanroom¹.

The calculation of the air supply for a non-unidirectional cleanroom is largely carried out by experience, educated guesswork and reference to suggested air change rates in ISO 14644-4⁴ and IEST RP 12⁵. This approach is unsatisfactory, and a method is required that is similar to calculating air supply rates from the heating and cooling loads. Models have been suggested⁶⁻⁸ but these need further development to include all relevant variables, as well as an assessment of the values assigned to these variables. Existing models calculate 'average' airborne concentrations, but there is also a need to calculate a 'maximum' concentration that is only exceeded on a small and defined proportion of occasions.

Total emission rate of airborne contamination

The sources of airborne particle contamination in cleanrooms are machinery and personnel, and the total emission rate is calculated as follows.

Equation 5

$$\text{Total emission rate} = \text{Emission rate per person} \times \text{No. of personnel} + \text{Emission rate from machinery}$$

There will also be some re-dispersion from the floor during walking, but in a typical cleanroom it is less than 1%⁹, and is disregarded in this article.

Dispersion rates from personnel in dispersal chambers

Dispersal chambers are used to measure airborne contamination from people, and it has been shown that dispersion rates vary between individuals, and from day-to-day. The average dispersal rates of 25 males and 30 females, when exercising in a dispersal chamber and wearing their

own indoor clothing, was measured by Whyte and Hejab³ and is given in **Table 1**. Also shown in **Table 1** is the effect of wearing a full set of cleanroom clothing over indoor clothing that was used by the same 55 people. The clothing consisted of a one-piece coverall manufactured from woven polyester fabric, hood, mask, latex gloves and overboots. The pore diameter of the clothing fabric, as determined by IEST Recommended Practise 3¹⁰ was 26 µm.

The dispersion rate, when wearing cleanroom clothing, varies considerably owing to the following.

- The more coverage of a person's body with cleanroom clothing, the lower the dispersion rate^{11, 12}. Gowns (smocks) are less effective than full sets of clothing owing to a lack of control of body emissions dispersed from below the gown, and poor designs of gowns may reduce the dispersion rate, in comparison to personal indoor clothing, by only 20%.
- The more effective the filtration properties of the fabric, such as obtained by tighter weaves of cloth, the more effective the clothing in preventing dispersion¹¹. New fabrics are more effective than used fabrics¹³.
- Fabrics used to manufacture cleanroom garments are more effective in filtering larger diameter particles (see **Table 1**). Therefore, the more effective the fabrics, the lower the concentration of MCPs in cleanrooms compared to particles.
- Garments worn under cleanroom clothing influence the dispersion rate of particles into the cleanroom, as the more particles generated by underclothing, the more that will pass through the outer cleanroom clothing. Undergarments made from fabrics that break-up easily, such as cotton and wool, emit more particles than poly-cotton clothing, which emit more particles than garments made of polyester or nylon. Moschner¹⁴ showed that individuals wearing a cotton track suit under cleanroom clothing dispersed about 10 times more particles than their own indoor clothing. However, as the main source of MCPs is skin and not clothing, underclothing fabric has a small effect on dispersion, although its filtration effectiveness against skin particles affects dispersion rates.
- The greater the activity of personnel, the greater the dispersion rate, and Moschner¹⁴ has shown that the dispersion rate of particles when exercising is about 20 times greater than when standing.

Dispersion rate from personnel working in a cleanroom

It is clear from dispersion chamber experiments that the dispersion of contamination from personnel varies

Table 1. Average dispersion rates/s from personnel in a dispersal chamber. Reduction given in parentheses.

Clothing worn	Particle type		
	≥0.5 µm	≥5 µm	MCPs
Own indoor clothing	35,500	5533	40
Full set cleanroom clothing: fabric pore diameter 26 µm	17,000 (2.1 times)	621 (8.9 times)	2.8 (14.2 times)

Table 2. Average dispersion rates/s per person.

Type of activity	Dispersion from one person/s		
	$\geq 0.5 \mu\text{m}$	$\geq 5 \mu\text{m}$	MCPs
Normal activity in cleanroom	908	46	0.017
Exercising in dispersal chamber	2170	550	0.13

according to activity and clothing. Activity in cleanrooms is normally lower than in a dispersion chamber, and the dispersion rate is likely to be lower. This was investigated.

Concentrations of airborne contamination were measured in the steady-state condition during normal manufacturing in a non-unidirectional airflow cleanroom (AstraZeneca, Macclesfield). There was no machinery, but some small items of equipment, e.g. air samplers and paper, would disperse some particles, but contamination was almost exclusively from two people working in the cleanroom. They wore a one-piece coverall made from high-quality polyester woven fabric with a pore diameter of $13 \mu\text{m}$, hood, overboots, face mask, goggles and latex gloves, which covered all skin areas. They worked at two Class IIB safety cabinets but occasionally moved about the room. The cleanroom's air supply was $0.75 \text{ m}^3/\text{s}$ and supplied by three rectangular ceiling inlets, without diffusers. Two inlets were directly above the cabinet's entrance and some of the supply air short-circuited into the cabinet's entrance. There was, therefore, less air supply available for mixing and diluting room air, and the air change effectiveness (ACE) index, which is discussed further in the "Ventilation effectiveness of supply air to cleanrooms" section, was measured using the method described by Whyte *et al*¹⁵, and found to be 0.44.

Concentrations of particles $\geq 0.5 \mu\text{m}$ and $\geq 5 \mu\text{m}$ were measured by sampling 1 ft^3 (28.3L) of room air each minute using a Lasair II® particle counter. The average count over four manufacturing sessions spread over 11 hours, was $2753/\text{m}^3$ for particles $\geq 0.5 \mu\text{m}$, and $139/\text{m}^3$ for particles $\geq 5 \mu\text{m}$. An average count of MCPs was obtained from 175 samples of 1 m^3 of room air sampled four times daily by a high efficiency, slit-to-agar AirTrace® sampler; 170 samples recovered no MCPs and five samples gave counts of 2, 1, 1, 3 and 2. The average result was, therefore, $0.05/\text{m}^3$. The total dispersion rate from the two people was calculated by means of Equation 6, and converted to a rate per person, and given in Table 2.

Equation 6

$$\text{Total dispersion rate/s} = \text{Air supply rate (m}^3/\text{s)} \times \text{ACE index} \times \text{Air concentration/m}^3$$

Also shown in Table 2 is the dispersion rate measured in a dispersal chamber from people wearing the same cleanroom clothing, and walking on the spot and moving their arms at a rate of 1/s. It may be seen that the dispersion rates in the cleanroom are much lower than in the dispersal chamber, presumably owing to greater activity.

It should be noted that the experimental method described above can be used to measure the dispersion rate of machinery and equipment, or the total dispersion rate from all sources in the cleanroom.

Particle dispersion from machinery

The emission rates of MCPs from machinery can be assumed to be zero in normal conditions, and only in rare and accidental circumstances will machines emit MCPs, e.g. a split hose spraying contaminated water. The emission rate of particles from machinery may be available from the manufacturer but can be obtained experimentally using the method described in the previous section. Some examples are given in Table 3^{16–18}.

Filter removal efficiency

In modern non-unidirectional cleanrooms, the removal efficiency of the high efficiency air filters ensures that the supply air will have an insignificant effect on the room's airborne contamination. High efficiency filters are classified in EN 1822-1¹⁹ and ISO 29463-1²⁰ by the most penetrating particle size. A typical filter used in non-unidirectional airflow cleanroom would have an overall removal efficiency of between 99.95% and 99.995%. As

Table 3. Particle dispersion from machinery.

Type of machine or equipment	Source of information	Emission rate/s
Vial filling machine A	Hejab ¹⁶	$3.3 \times 10^4/\text{s}$ particles $\geq 0.5 \mu\text{m}$
Vial filling machine B	Hejab ¹⁶	$5 \times 10^2/\text{s}$ particles $\geq 0.5 \mu\text{m}$
Blow-fill-seal (BFS) machines	Sundstrom, Ljungqvist and Reinmuller ¹⁸	Between 10^2 and 10^7 particles $\geq 0.5 \mu\text{m}/\text{s}$, depending on type of BFS machinery
Six-axis robot – unmodified – modified to reduce emission	Hnatek ¹⁷	Unmodified robot: $4 \times 10^3/\text{s}$ of particles $\geq 0.5 \mu\text{m}$ Modified robot: $0.3/\text{s}$ of particles $\geq 0.5 \mu\text{m}$

most of the air supplied to a cleanroom is recirculated from the cleanroom, only 0.05% to 0.005% of the airborne contamination in the cleanroom will come with the supply air. It can, therefore, be assumed that if typical high efficiency filters are installed, their effect can be ignored in the calculation of the air supply rate. However, should the efficiency of the filters be lowered to include, for example, an energy-efficiency design, then this can be investigated by a more rigorous approach^{8,21}.

Ventilation effectiveness of supply air to cleanrooms

Studies of the ventilation effectiveness of the air supply in non-unidirectional airflow cleanrooms have reported imperfect mixing of the air supply and room air, and a variation in airborne contamination at different locations within the cleanroom^{15,23}. The ventilation effectiveness at a location can be given by an ACE index, as described by ANSI/ASHRAE 129 Standard²², and calculated in cleanrooms by the method described by Whyte *et al*¹⁵ using the following equation.

Equation 7

$$\text{ACE index} = \frac{\text{Measured air change rate at a location}}{\text{Average air change rate in cleanroom}}$$

The 'measured air change rate at a location' is obtained by measuring the decay rate of test particles at a location and use of Equation 8 or 9. The air change rate at the location is equal to the decay rate.

Equation 8

$$N = -\frac{1}{t} \ln \frac{C}{C_i}$$

Or, alternatively,

Equation 9

$$N = -2.3 \cdot \frac{1}{t} \log_{10} \left(\frac{C}{C_i} \right)$$

Where, N = decay rate of particles = air change rate at measuring location, t = time of decay, C = airborne concentration of particles after a given decay time, C_i = initial airborne concentration of particles.

The room's average air change rate is obtained by dividing the room's overall air supply rate by the room's volume, although it may also be obtained from volume-weighted decay rates measured at the air extracts.

If the cleanroom air is perfectly mixed, the ACE index will have a value of 1 at all locations, and the concentration of airborne contamination during manufacture will be even throughout the cleanroom. If the ACE index is greater than 1, then more clean air supply will reach the test location than average, and the airborne particle concentration will be lower. If the ACE index is

lower than 1 then the opposite is true. Thus, a lower ACE index shows that important locations, such as test points used to demonstrate that the cleanroom complies to ISO 14644-1, or areas where product is open to airborne contamination during manufacture, may have airborne contamination concentrations higher than average, and that the air supply rate needs to be raised to ensure that the required conditions are met. The following Equations 10 and 11 are derived from Equations 2 and 3 to incorporate the ACE index.

For small particles unaffected by gravity:

Equation 10

$$Q_s = \left[\frac{D}{C} \right] / \text{ACE}$$

Where ACE is the local air change effectiveness index.

For larger particles affected by gravity, such as airborne MCPs:

Equation 11

$$Q_s = \left[\frac{D}{C} - V_D \cdot A \right] / \text{ACE}$$

Effect of clean air devices

Cleanrooms may contain clean air devices, such as unidirectional airflow workstations or isolators, to provide zones of high-quality clean air. Where these devices discharge filtered air into the cleanroom, airborne contamination will be reduced and the rate of clean air supply, needed for a given airborne concentration, is, therefore, less.

Some clean air devices have air supplied by an air conditioning plant outside the cleanroom, and others draw air from the cleanroom. Shown in **Figure 1** is a typical airflow pattern produced by a unidirectional airflow clean air device that draws air from the cleanroom. This was obtained by the computational fluid dynamics (CFD) technique described by Whyte *et al*²³. The CFD analysis was carried out in three dimensions but only a thin cross-sectional plane is shown in **Figure 1**. The magnitude and direction of the air velocity is given by the colour of the lines and arrows, the highest velocity being red and, as the velocity drops, the colours move from yellow to green, and then to blue.

In the example shown in **Figure 1**, the room's air supply diffusers are not directly over the clean air device's intake, but some supply air is drawn into the device and does not enter the room's air circulation. Also, air exiting the device passes along the floor and may enter low-level extracts without effectively mixing and diluting the airborne contamination within the cleanroom. Although it does not noticeably occur in this example, air exiting from the device can short-circuit back to the device's air intake.

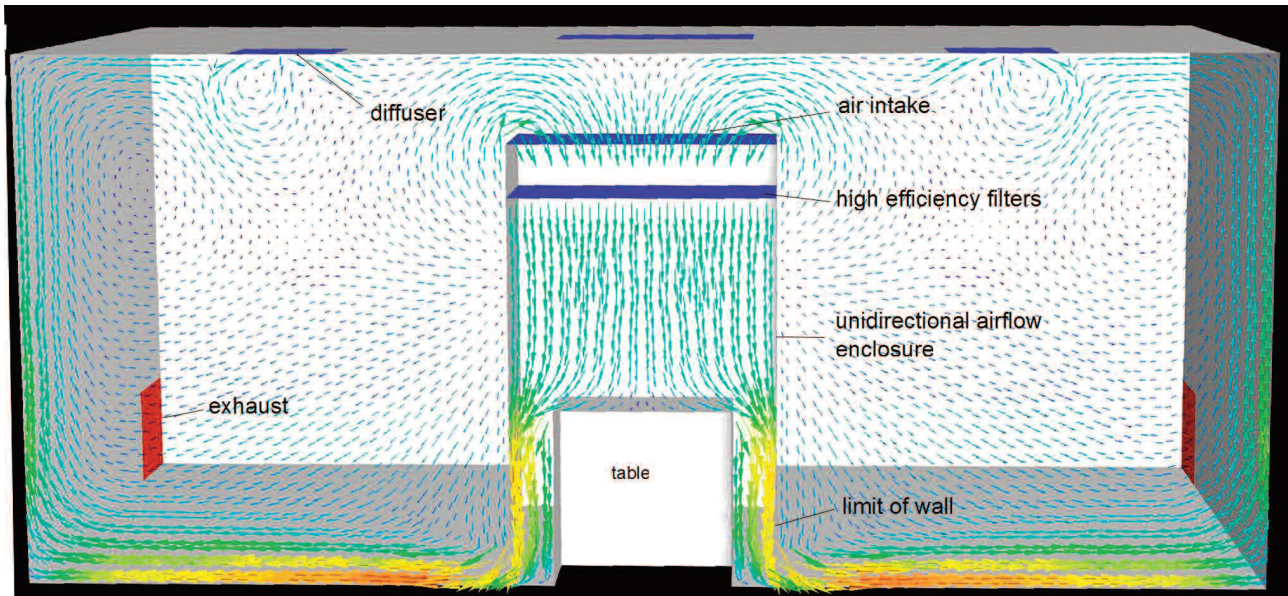


Figure 1. Airflow from a unidirectional clean air device in a non-unidirectional airflow cleanroom.

These three types of short-circuiting will reduce the proportion of air from the device that may contribute to the dilution of the airborne contamination in the cleanroom.

The proportion of air that passes through a clean air device and effectively dilutes cleanroom air can be described by a ventilation effectiveness coefficient (β). For example, if β is 0.5, then half of the device's air is considered to perfectly mix and dilute room air, and the other half not to mix at all. Therefore, the cleanroom's air supply rate can be reduced by an amount equivalent to 0.5 of the air volume supply rate that passes through the device.

Some preliminary experiments have been carried out to establish the value of β , and indicate that in situations similar to **Figure 1**, it will be about 0.5. However, if a unidirectional airflow workstation obtains its air from the main air conditioning plant, much of the device's discharged air will enter the room's low-level extracts, and β may be about 0.2. Where clean air devices are small and allow the air entering and exiting devices to effectively mix with room air, β will be around 0.8.

To calculate the air flow supply rate required for a non-unidirectional airflow cleanroom, when a clean air device is present, Equations 12 and 13 should be used.

For small particles unaffected by gravity:

Equation 12

$$Q_S = \frac{D}{C \cdot ACE} - \beta Q_D$$

Where β is the ventilation efficiency coefficient of the clean air device, and Q_D is the air supply volume passing through the clean air device.

For MCPs deposited by gravity:

Equation 13

$$Q_S = \frac{D}{C \cdot ACE} - V_D \cdot A - \beta Q_D$$

Air supply rate to ensure the required airborne concentration in cleanrooms is rarely exceeded

Previous sections of this article describe a method used to calculate the air supply rate that is based on average emission rates from sources of contamination in the room, and predicts an 'average' concentration. This may be satisfactory in some cleanrooms, but in many cleanrooms it will be considered unsatisfactory, as ISO 14644-1²⁴ classifies cleanrooms by the 'maximum' airborne concentration of particles.

Specifying a 'maximum' concentration implies that there should be no airborne count higher than the maximum. However, the distributions of airborne counts obtained in cleanrooms are of the type shown in **Figures 2, 3 and 4**, and there will always be a chance of a count higher than a 'maximum', although the probability will be small. It is more correct to specify a concentration that should not be exceeded, except on a small and defined proportion of occasions.

Figures 2, 3 and 4 show three frequency distributions of counts where the ratio of standard deviation (σ) to mean (μ) varies. These ratios can be defined by coefficients of variation (C_v), where,

$$C_v = \sigma/\mu.$$

Figures 2, 3 and 4 have distributions with a C_v of about 0.5, 1 and 2, respectively, and encompass the range normally found throughout cleanrooms. The distributions have a

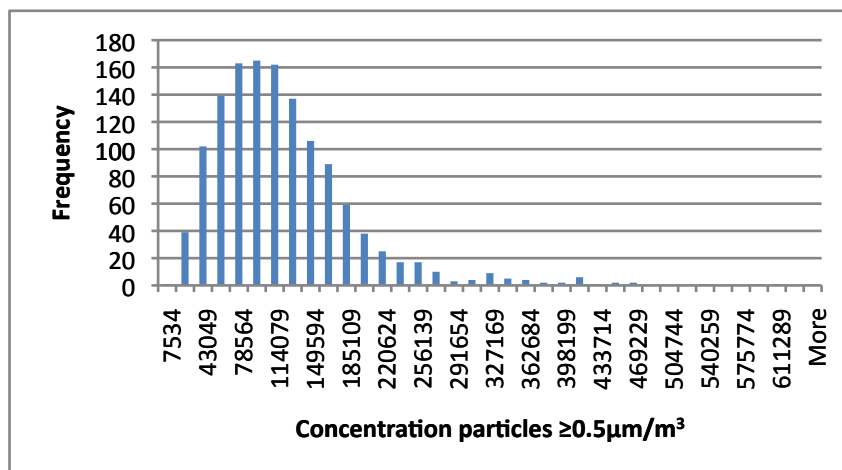


Figure 2. Distribution of airborne counts of particles $\geq 0.5 \mu\text{m}/\text{m}^3$ in cleanroom 1. Mean = 114,971, standard deviation = 73,234.

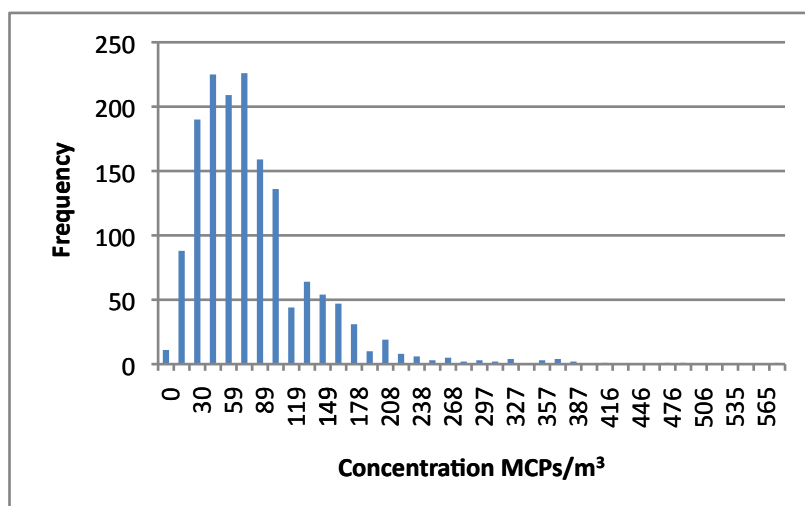


Figure 3. Distribution of airborne counts of MCPs/m³ in cleanroom 1. Mean = 60, standard deviation = 60.

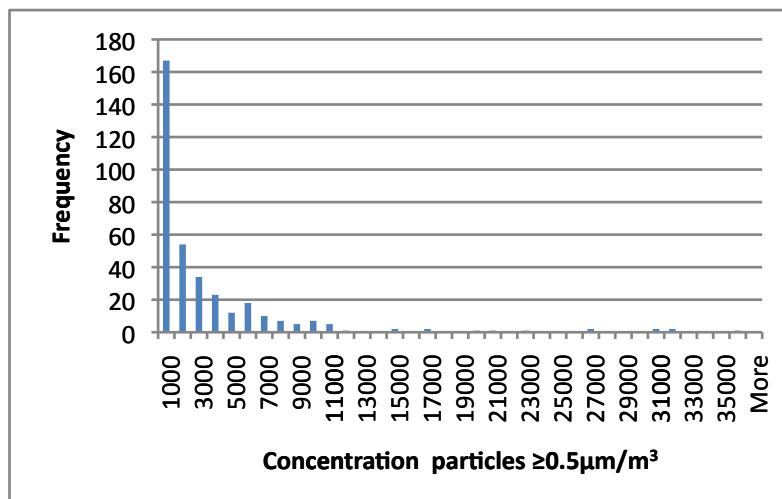


Figure 4. Distribution of airborne counts of particles $\geq 0.5 \mu\text{m}/\text{m}^3$ in cleanroom 2. Mean = 3027, standard deviation = 5208.

positive skew with an extended tail containing high counts. In addition, **Figure 4** shows the type of distribution obtained in high-quality cleanrooms where zero counts are registered. Distributions of airborne counts are often treated as a Normal (Gaussian) distribution, although cleanroom users are generally aware that log-normal, Poisson or negative-binomial distributions are often a better choice.

The ‘maximum’ count of a count frequency distribution can be defined in terms of an upper percentile value, e.g. the 95th percentile, which gives the percentage of counts that are expected to be below the ‘maximum’ count. After the percentile is selected, the Z-value, which is the number of standard deviations the percentile is from the mean, can be obtained. It is convenient to choose a percentile corresponding to a Z-value that is a whole number. In a Normal distribution, the 97.7th percentile has a Z-value of 2, i.e. it is two standard deviations above the mean, and the 99.9th percentile has a Z-value of 3. However, any suitable percentile for a Normal distribution can be chosen, such as the 95th or 99th, with Z-values of 1.65 and 2.33, respectively, and various one-sided Z-values are obtained from a reference source, such as, <http://www.measuringusability.com/zcalcp.php>.

In a Normal distribution with mean μ and standard deviation σ , the ‘maximum’ concentration (C) that corresponds to Z is,

Equation 14

$$C = \mu + \sigma.Z$$

Therefore, if a ‘maximum’ concentration (C) of airborne contamination is required in preference to an ‘average’ concentration (μ), the air supply rate to the cleanroom will have to be increased N times, where,

Equation 15

$$N = C/\mu = 1 + C_v.Z$$

Given in **Table 5** are examples of the number of times the air change rate should be increased to obtain a ‘maximum’ concentration instead of an ‘average’ concentration, for different percentiles and coefficients of variation.

Setting the percentile at the 95th or 97.7th value will be acceptable in many industries. This is particularly so when it is understood that, when a count above the maximum acceptable concentration is recorded, the compliance method given in ISO 14644-1²⁴ allows a retest, and the chance of obtaining two consecutive failures above the maximum is, in the case of the 97.7th percentile, $0.023 \times 0.023 = 0.0005$, i.e. 1 in 2000. However, in industries with strict cleanliness requirements, a higher percentile can be used, e.g. the 99th or 99.9th.

Practical example of the calculation of the air supply rate for a required airborne concentration of contamination

No cleanroom has been designed using the method described in this article, but the validity of the method can

Table 5. Required increase in air supply rate.

Percentile	Z	C _v	Increase in air rate (N)
95th	1.65	0.5	1.8 times
	1.65	1	2.7 times
	1.65	2	4.3 times
97.7th	2	0.5	2 times
	2	1	3 times
	2	2	5 times
99th	2.33	0.5	2.2 times
	2.33	1	3.3 times
	2.33	2	5.7times
99.9th	3	0.5	2.5 times
	3	1	4 times
	3	2	7 times

be ascertained by using an actual cleanroom to compare the airborne concentrations produced from the known air supply rate and the calculated air supply.

The non-unidirectional airflow cleanroom used as an example had a large floor area (1280 m²) and contained no clean air devices. The airborne concentration required, in operational conditions, for particles $\geq 0.5 \mu\text{m}$ was 3,520,000/m³, and for MCPs it was 100/m³. The cleanroom had an air supply rate of 21.6 m³/s, which was supplied through HEPA filters and 4-way diffusers in the ceiling and removed through low-level extracts. This gave reasonable mixing of room and supply air, and using the information published by Whyte *et al*¹⁵, the ACE index was assumed to be 0.8.

Seventy people worked in the cleanroom and wore cleanroom gowns over their own indoor clothing, along with caps and overshoes. They continually worked in the sitting or standing position, or walked about the room. Because of this relatively high activity and clothing worn, the average dispersion rate of particles $\geq 0.5 \mu\text{m}$ was assumed to be 35,500/s, and for MCPs it was 20/s. The total dispersion rate from 70 people for particles $\geq 0.5 \mu\text{m}$ was, therefore, $2.5 \times 10^6/\text{s}$, and for MCPs it was 1400/s.

The air supply volumes (Q_s) needed to achieve the required concentrations, as an ‘average’ value, can be calculated by Equation 9 and 10. Had the cleanroom contained a clean air device, then Equations 10 and 11 would have been used.

For particles, $\geq 0.5 \mu\text{m}$:

$$Q_s = \left[\frac{D}{C} \right] / \text{ACE} = \frac{2.5 \times 10^6}{3.52 \times 10^6} / 0.8 = 0.89 \text{ m}^3/\text{s}$$

For MCPs:

$$Q_s = \left[\frac{D}{C} - V_D \cdot A \right] / \text{ACE} = \frac{1400}{100} - (0.0046 \times 1280) / 0.8 = 10.1 \text{ m}^3/\text{s}$$

These calculations show that more air supply is required to achieve the correct airborne concentration of MCPs than for particles, and the required supply rate to the cleanroom would have to be 10.1 m³/s.

The accuracy of the above calculation can be checked by using the actual air supply rate and airborne MCP counts found in the cleanroom. Samples (1560) were taken of MCP concentrations and they averaged 60/m³. The actual air supply to the cleanroom was 21.6 m³/s, and as the average airborne concentration is in proportion to the air supply rate, a reduction in the air supply to the calculated 10.1 m³/s would increase the airborne MCP concentration by 2.14 fold, to give an expected average concentration of 128/m³. This is higher than the required 100/m³, and probably reflects an over-estimation of the dispersion rate.

The air supply rate required for a 'maximum' concentration of 100 MCPs/m³ can now be calculated. It was known that in similar cleanrooms, the standard deviation of the counts was similar to the mean, and a C_v of 1 was assumed. The 97.7th percentile was chosen and, therefore, as shown in **Table 5**, the air supply should be increased 3-fold over that calculated for an 'average' concentration, i.e. to 30.3 m³/s. The accuracy of the calculation can be verified by determining the concentration of the air samples where 97.7% of the MCP air counts were lower. This was found to be 225/m³ for an actual air supply rate of 21.6 m³/s. If the air supply rate was the same as that calculated, then it would have to be increased by 1.4 times, and the expected airborne concentration would be 1.4 times lower, i.e. 161/m³. This result is again greater than the required concentration of 100/m³, and likely to be caused by an over-estimate of the dispersion rate, but also by statistical assumptions.

It has been assumed that the MCP counts conform to a Normal distribution, but a log-normal distribution may be a better assumption. This means that the log of MCP count values conform to a Normal distribution. Using μ and σ to denote the mean and standard deviation of the Normal distribution of the MCP counts, the mean (α) and standard deviation (β) of the log MCP count distribution can be calculated as follows:

$$\beta = \sqrt{\ln \left[1 + \left(\frac{\sigma}{\mu} \right)^2 \right]} = \sqrt{\ln \left[1 + \left(\frac{100}{100} \right)^2 \right]} = 0.83$$

$$\alpha = \ln(\mu) - \frac{\beta^2}{2} = \ln(100) - \frac{0.83^2}{2} = 4.6 - 0.344 = 4.26$$

The mean of the log-normal distribution for the MCP counts is $\exp(\alpha + \beta^2/2)$ and the percentiles are in the form $\exp(\alpha + \beta Z)$. Therefore, as in Equation 13, the increase in air supply rate over that required for a 'maximum' concentration is:

$$N = C/\mu = \exp(\alpha + \beta Z)/\exp(\alpha + \beta^2/2) = \exp(\beta Z - \beta^2/2) = \exp(0.83 \times 2 - (0.83)^2/2) = 3.73$$

A 3.73 increase in the air supply rate to 37.7 m³/s is, therefore, anticipated by a log-Normal distribution. This is

1.75 times greater than the actual air supply, and, therefore, the expected 'maximum' airborne concentration would be 1.75 times less, at 129/m³. This result is closer to the required concentration of 100/m³ than that calculated using a Normal distribution.

Discussion

The method often used, at present, to obtain the required air supply rate for non-unidirectional cleanrooms is based on experience and educated guesswork. This often leads to an over-specification of the air supply rate, with lower airborne concentrations of contamination than necessary, and a considerable waste of energy. This article suggests a method to improve the accuracy of the method, and highlights the importance of the variables that influence the calculation.

The method makes the reasonable assumption that typical high efficiency filters used in cleanrooms remove most of the contamination in the supply air. It also assumes that positive pressurisation of the cleanroom ensures a minimum ingress of contamination from adjacent areas. The required air supply rate can then be calculated by use of steady-state equations that consider the surface deposition of larger particles, such as MCPs, and the following variables:

- (a) dispersion rate of airborne contamination from personnel and machinery,
- (b) effectiveness of the air supply distribution,
- (c) dilution of airborne contamination by clean air devices,
- (d) variability of the airborne concentrations.

A review of the rates of dispersion of contaminants from people studied in dispersal chambers shows that these vary according to activity and type of clothing, and to obtain accurate rates it is best to obtain these in cleanrooms during actual or simulated manufacturing, using the method described in the "*Dispersion rate from personnel working in a cleanroom*" section. The emission rate of airborne contamination from machinery must be included in the total dispersion rate. Surprisingly, few particle emission rates are available from manufacturers, although it is relatively easy to obtain these by means of the method discussed in the "*Dispersion rate from personnel working in a cleanroom*" section.

The ventilation effectiveness of the air supply should be considered, as good air mixing in non-unidirectional cleanrooms cannot be assumed, and the concentration of airborne contamination may vary about the room. When compliance testing is carried out according to ISO 14644-1²⁴, or concentrations measured at important locations, test points may coincide with areas of higher airborne concentrations. It will, therefore, be necessary to upwardly adjust the air supply rate to compensate, using the method discussed in the "*Ventilation effectiveness of supply air to cleanrooms*" section.

The calculated air supply rate will be decreased by clean air devices that discharge filtered air into a cleanroom. Not all of the air from a device will effectively

mix and dilute cleanroom air, and it is necessary to know the proportion that contributes. This is discussed in the “Effect of clean air devices” section.

The method described in the first part of this article calculates the air supply rate required to obtain an ‘average’ concentration of airborne contamination. An ‘average’ concentration may be acceptable, but it may be necessary to design for a ‘maximum’ concentration that will only be exceeded on a defined and low probability. Using knowledge of the ratio of the standard deviation to the mean, and the requirement for the ‘maximum’ concentration in terms of an upper percentile of the count distribution, the required increase in the supply air rate can be calculated. A practical example has been included to illustrate the method, including the use of a log normal distribution of the count as an alternative to a Normal distribution.

The suggested method of calculating the air change rate will be as accurate as the input data. Further research is required on the dispersion rates of airborne contamination from personnel and machinery in cleanrooms, the effectiveness of the air supply, the effect of clean air devices, and the best statistical distributions to ensure that a given ‘maximum’ count is rarely exceeded. However, estimates of variables given in this article should give a higher degree of accuracy than presently available, and enable a better understanding of the relationship of air supply rates to the variables that affect it.

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References

- Whyte W, Whyte WM and Eaton T. The application of the ventilation equations to cleanrooms; Part 1: The equations. *Clean Air and Containment Review* 2012; Issue 12:4–8.
- Whyte W. Sterility assurance and models for assessing airborne bacterial contamination. *Journal of Parenteral Science and Technology* 1986; **40**:188–197.
- Whyte W and Hejab M. Particle and microbial airborne dispersion from people. *European Journal of Parenteral and Pharmaceutical Science* 2007; **12**(2):39–46.
- International Organization for Standardization. *ISO 14644-4: 2001. Cleanrooms and Associated Controlled Environments—Part 4: Design, Construction and Start-up*. Geneva, Switzerland: ISO; 2001.
- Institute of Environmental Science and Technology. *IEST RP-CC012 Considerations in Cleanroom Design*. Arlington Heights, USA: IEST; 2007.
- Zhang J. Understanding pharmaceutical cleanroom design. *ASHRAE Journal* 2004; September:29–32.
- Wei S, Mitchell J, Flyzik K, Shih-Cheng H, Junjie L, Vijayakumar, R and Fukuda H. Development of cleanroom required airflow rate model based on establishment of theoretical basis and lab validation. *ASHRAE Transactions* 2010; **116**(1):87–97.
- Camfil Farr. Report: Clean room design standards and energy optimization. Stockholm, Sweden: Camfil Farr; 2012. Available at: <https://www.camfil.com/Filter-technology/Camfil-Farr-Software/CREO-Software/>.
- Whyte W, Whyte WM, Blake WM and Green G. Dispersion of microbes from floors when walking in ventilated rooms. *International Journal of Ventilation* 2013; **12**(3):271–284.
- Institute of Environmental Science and Technology. *IEST RP-CC003. Garment System Considerations for Cleanrooms and Other Controlled Environments*. Arlington Heights, USA: IEST; 2011.
- Whyte W and Bailey PV. Reduction of microbial dispersion by clothing. *Journal of Parenteral Science and Technology* 1985; **39**(1):51–61.
- Whyte W and Bailey PV Particle dispersion in relation to clothing. *Journal of Environmental Sciences* 1989; **32**:43–49.
- Ljungqvist B and Reinmuller B. People as a contamination source: cleanroom clothing systems after 1, 25 and 50 washing/sterilisation cycles. *European Journal of Parenteral and Pharmaceutical Sciences* 2003; **8**(3):75–79.
- Moschner C. Study into human particle shedding. *Cleanroom Technology* 2011; August:25–33.
- Whyte W, Ward S, Whyte WM and Eaton T. The decay of airborne contamination and ventilation effectiveness in cleanrooms. *International Journal of Ventilation* 2014; **13**(3):211–219.
- Hejab M. Prediction of airborne contamination in conventionally-ventilated cleanrooms. PhD Thesis, University of Glasgow, Scotland; 1992.
- Hnatel ER. *Integrated Circuit Quality and Reliability*. Second edition. Boca Raton, FL: CRC Press; 1995.
- Sundstrom S, Ljungqvist B and Reinmuller B. Some observations on airborne particles in blow-fill-seal filling rooms. *PDA Journal of Pharmaceutical Science and Technology* 2007; **61**(3):147–153.
- European Commission. *EN 1822-1: 2009. High Efficiency Air Filters (EPS, HEPA, and ULPA) – Part 1. Classification, Performance Testing and Marking*. Brussels, Belgium: European Commission, Enterprise and Industry DG; 2009.
- International Organization for Standardization. *ISO 29463-1. High-Efficiency Filters and Filter Media for Removing Particles in Air – Part 1: Classification, Performance Testing and Marking*. Geneva, Switzerland: ISO; 2011.
- Whyte W, Green G and Whyte WM Removal of microbe-carrying particles by high efficiency air filters in cleanrooms. *International Journal of Ventilation* 2013; **10**(4):339–351.
- American Society of Heating, Refrigerating and Air Conditioning Engineers. *ANSI/ASHRAE Standard 129-1997 (RA 2002). Measuring Air-Change Effectiveness*. Atlanta, USA: ASHRAE; 2002.
- Whyte W, Hejab M, Whyte WM and Green G. Experimental and CFD airflow studies of a cleanroom with special respect to air supply inlets. *International Journal of Ventilation* 2011; **9**:197–210.
- International Organization for Standardization. *ISO 14644-1. Cleanrooms and Associated Controlled Environments – Part 1: Classification of Air Cleanliness*. Geneva, Switzerland: ISO; 1999.